

**Amendments to the Specification:**

Please replace the paragraph beginning at page 2, line 9, with the following:

--Peptide 35 (also called peptide 88) has the amino acid sequence RLRRICSGILLIRILGIFV (SEQ ID NO:1), optionally with a vector-derived sequence RPVR (SEQ ID NO:2) or RPVRP (SEQ ID NO:3) at the C-terminus. Peptide 38 has the amino acid sequence TSGLLKL VQAKRKCCIS (SEQ ID NO:4). Peptide 40 has the amino acid sequence RWDPTRLLRFRFLRMLVRRS (SEQ ID NO:5), optionally with a vector-derived sequence RPVR (SEQ ID NO:2) or RPVRP (SEQ ID NO:3) at the C-terminus. Peptide 41 has the amino acid sequence GRGCIFRWRRGLRGMMRLFK (SEQ ID NO:6). The peptides optionally have lysine residues fused to the N-terminus (e.g., 7 lysine residues; SEQ ID NO:7).--

Please replace the paragraph beginning at page 2, line 16, with the following:

--The nucleotide sequences encoding the peptides are

Peptide 35/88:

CGGCTCCGGAGAATATGTAGCGGCATTCTGCTCATCCGTAGGATATTGGGCATTTTC  
GTTAGGCCCGTGAGGCCCTAA (SEQ ID NO:8)

Peptide 38:

ACTAGTGGGTTGCTGAAGCTGGTGCAGGCTAAGCGTAAGTGTTGTATTAGTTA (SEQ ID NO:9)

Peptide 40:

CGTTGGGATCCGACGCGATTGCTGCGATTTCGGTTCCTCCGGATGCTAGTGAGGCGG  
AGTAGGCCCGTGAGGCCCTAA (SEQ ID NO:10)

Peptide 41:

GGAAGGGGATGTATCTTTTCGATGGAGGAGAGGCCTGCGGGGAATGATGAGACTATT  
TAAGTAG (SEQ ID NO:11)--

Please replace the paragraph beginning at page 3, line 11, with the following:

--In one embodiment, the invention provides a peptide comprising at least 14 amino acids, comprising at least 5 arginine residues (SEQ ID NO:24), and having a motif X(2-3 aa)X'(2-3 aa) X''(1 aa)X''' (SEQ ID NO:12), wherein X, X', X'', and X''' are individually large hydrophobic amino acid selected from the group consisting of L, I, F, M, Y, W, and wherein at least one is L or I.--

Please replace the paragraph beginning at page 3, line 17, with the following:

--Figure 1 shows an SDS gel of the affinity extract for peptide 40 and its inactive mutant. This peptide blocks the cell cycle of A549 cells. Biotinylated peptide 40 is fused to the C-terminus of GFP with a linker EEAAKA (SEQ ID NO:13) (biotin-GMDELYK-EEAAKA-RWDPTLLRFRFLRMLVRRSRpvr; SEQ ID NO:14). Also tested is inactive a biotinylated alanine mutant biotin-GMDELYK-EEAAKA-RWDPTRALRARFARALVRRSRpvr (SEQ ID NO:15). The difference bands were identified by MALDI-time of flight mass spectrometry. This peptide affinity extracts beta tubulin, importin beta 1 and 3 (and all or part of the nuclear pore complex), elongation factor tu, an ATP/ADP carrier protein, and a zinc finger protein.--

Please replace the paragraph beginning at page 3, line 25, with the following:

--Figure 2 shows an SDS gel of the affinity extract for peptide 41 and its inactive mutant. This peptide blocks the cell cycle of A549 cells. Peptide 41 is fused to the C-terminus

of GFP with a linker EEAACA (SEQ ID NO:13) (GMDELYK-EEAACA-GRGCIFRWRRGLRGMMRLFk; SEQ ID NO:16). The difference bands were identified by MALDI-time of flight mass spectrometry. This peptide affinity extracts beta tubulin, portion beta subunits 1, 3, and 7, annexin II, calpactin/S-100, and chaperoninBip/GRP78.--

Please replace the paragraph beginning at page 4, line 3, with the following:

--Figure 5 shows nucleotide and amino acid sequences of #38, #40, #41, and #88 (SEQ ID NOS:17, 14, 10, 18, 11, 6, 8 and 19, respectively). The amino acid sequences and the in-frame stop codon in each peptide are indicated as bold letters. The vector sequence is underlined.--

Please replace the paragraph beginning at page 4, line 17, with the following:

--Figure 8 shows variants of synthetic #40 and 41 (SEQ ID NOS:20-23). The peptides with seven Lys (SEQ ID NO:7) and linker (GGEEAACA; SEQ ID NO:25) in N-terminus were synthesized (New England Peptide Inc, (K7\_#40, K7\_#40M, K7\_#41, and K7\_#41M). Mutated residues were underlined.--

Please replace the paragraph beginning at page 5, line 16, with the following:

--Figure 14 shows biotin-peptide affinity extracts examined by 1D SDS-PAGE and Western blotting. Lysates of ca.  $10^8$  A549 cells, treated with a protease inhibitor cocktail, were affinity extracted with biotin-GMDELYKEEAACA-peptide 40, 41 and 35 in separate experiments (GMDELYKEEAACA = SEQ ID NO:26). Peptides with the four leucine-rich motif residues mutated to alanine, which were inactive, were used as controls. Bands present at higher levels in the active peptide affinity extract compared to the mutant peptide extract are

labeled. Each peptide extracted 5-6 noticeable bands, some of which were common to more than one peptide extract. The largest band, 4, was identified as beta-tubulin by MALDI-TOF mass spectrometry; band 2 was identified as an importin beta subunit.--

Please replace the paragraph beginning at page 37, line 33, with the following:

--Common linkers such as peptides, polyethers, and the like can also serve as tags, and include polypeptide sequences, such as poly gly Gly sequences of between about 5 and 200 amino acids (SEQ ID NO:27). Such flexible linkers are known to persons of skill in the art. For example, ~~poly(ethylene glycol)~~ poly(ethylene glycol) linkers are available from Shearwater Polymers, Inc. Huntsville, Alabama. These linkers optionally have amide linkages, sulfhydryl linkages, or heterofunctional linkages.--

Please replace the paragraph beginning at page 51, line 27, with the following:

--As shown in figure 5, the cDNA inserts of #38, #40, #41 and #88 encode 17mer, 24mer, 20mer, 24mer peptides, respectively. #40 and #88 have the additional amino-acid sequence (RPVRP; SEQ ID NO:3) derived from the vector due to deletion of one nucleotide in the randomized region of the peptides.--

Please replace the paragraph (Table 1.) beginning at page 53, line 1, with the following:

**--Table 1. Effect of GFP fusion peptides and their mutants**

Peptide	Sequence	<u>SEQ</u> <u>ID NO:</u>	Growth Ratio (mean $\pm$ SE)
GFP-random 20mer fusion			1.1 $\pm$ 0.1
dsGFP			1.1 $\pm$ 0.1
p21C	KRRQTSMTDFYHSKRRLIFSKRKP	<u>28</u>	4.5 $\pm$ 0.8
#40	RWDPTRLLRFRFLRMLVRRSRPVRP	<u>18</u>	2.4 $\pm$ 0.3
#40(M15A)	RWDPTRLLRFRFLR <u>A</u> LVRRSRPVRP	<u>29</u>	2.0
#40(L13A/M15A)	RWDPTRLLRFRF <u>A</u> R <u>A</u> LVRRSRPVRP	<u>30</u>	1.6 $\pm$ 0.2
#40(F10A/L13A/M15A)	RWDPTRLLR <u>A</u> R <u>F</u> <u>A</u> R <u>A</u> LVRRSRPVRP	<u>31</u>	1.3 $\pm$ 0.1
#41	<del>GRGCIFRWRRGLRGMMRAFK</del> <u>GRGCIFRWRRGLRGMMRLFK</u>	<u>6</u>	2.7 $\pm$ 0.2
#41(L18A)	GRGCIFRWRRGLRGMMR <u>A</u> FK	<u>32</u>	1.7
#41(M16A/L18A)	GRGCIFRWRRGLRGMA <u>R</u> AFK	<u>33</u>	1.5
#41(L12A/M16A/L18A)	GRGCIFRWRRG <u>A</u> RGMA <u>R</u> AFK	<u>34</u>	1.1 $\pm$ 0.1
#88	RLRRICSGILLIRRLGIFVRPVRP	<u>19</u>	2.7 $\pm$ 0.4
#88(I18A)	RLRRICSGILLIRRLG <u>A</u> FVRPVRP	<u>35</u>	1.5
#88(L16A/I18A)	RLRRICSGILLIRRI <u>A</u> G <u>A</u> FVRPVRP	<u>36</u>	1.1
#88(I12A/L16A/I18A)	RLRRICSGILL <u>A</u> RR <u>I</u> AG <u>A</u> FVRPVRP	<u>37</u>	1.1 $\pm$ 0.1
HIV1 REV	<u>L</u> PP- <u>L</u> -ER <u>L</u> T <u>L</u> D	<u>38</u>	
MAPKK	<u>L</u> QKK <u>L</u> -EE <u>E</u> <u>L</u> <u>E</u> <u>L</u> D	<u>39</u>	
HTLV1 Rex	<u>L</u> SAQ <u>L</u> YSS <u>L</u> <u>S</u> <u>L</u> D	<u>40</u>	

Hdm-2	<u>I</u> SL <u>S</u> F <u>D</u> ES <u>L</u> AL <u>C</u>	<u>41</u>	
PKI	<u>L</u> AL <u>K</u> L-AG <u>L</u> D <u>I</u> N	<u>42</u>	
#40	RWD <u>P</u> TR <u>L</u> LR-F-R <u>F</u> L <u>R</u> M <u>L</u> VRRSRPV <u>R</u> P	<u>18</u>	
#41	GRGCIFRWRRGLRGMM <u>R</u> L <u>F</u> K	<u>6</u>	
#88	RLRRICSG <u>I</u> LL- <u>I</u> RR <u>I</u> L <u>G</u> IFVRPV <u>R</u> P	<u>19</u>	

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Please replace the paragraph (Table 2.) beginning at page 54, line 10, with the following:

**--Table 2. Effect of GFP fusion peptides and their mutants**

Peptide	Sequence	<u>SEQ ID</u> <u>NO:</u>	Growth Ratio (mean ± SE)
GFP-random 20mer fusion			1.1 ± 0.1
dsGFP			1.1 ± 0.1
p21C	KRRQTSMTDFYHSKRRLIFSKRKP	<u>28</u>	4.5 ± 0.8
#38	TSGLLKL <u>V</u> QAKRKCCIS	<u>4</u>	2.5 ± 0.2
CDC42C	<u>A</u> ALEPPET <u>Q</u> PKRKCC <u>I</u> <u>F</u>	<u>43</u>	1.3 ± 0.1
#38NΔ(1-8)	QAKRKCCIS	<u>44</u>	1.5 ± 0.1
#38NΔ(1-13)	CCIS	<u>45</u>	1.2 ± 0.1
#38(T1A)	<u>A</u> SGLLKL <u>V</u> QAKRKCCIS	<u>46</u>	3.5 ± 0.2
#38(S2A)	T <u>A</u> GLLKL <u>V</u> QAKRKCCIS	<u>47</u>	5.5 ± 0.8
#38(G3A)	TS <u>A</u> LLKL <u>V</u> QAKRKCCIS	<u>48</u>	2.7 ± 0.2
#38(L4A)	TSG <u>A</u> LKL <u>V</u> QAKRKCCIS	<u>49</u>	2.2 ± 0.1
#38(L5A)	TSGL <u>A</u> KL <u>V</u> QAKRKCCIS	<u>50</u>	1.9 ± 0.2
#38(K6A)	TSGLL <u>A</u> L <u>V</u> QAKRKCCIS	<u>51</u>	1.4 ± 0.1
#38(L7A)	TSGLLK <u>A</u> <u>V</u> QAKRKCCIS	<u>52</u>	2.0 ± 0.2
#38(V8A)	TSGLLK <u>L</u> <u>A</u> QAKRKCCIS	<u>53</u>	2.7 ± 0.2
#38(C14A)	TSGLLKL <u>V</u> QAKRK <u>A</u> CIS	<u>54</u>	1.1 ± 0.1

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Please replace the paragraph beginning at page 58, line 26, with the following:

--In order to examine whether it is necessary to express the peptides with the protein scaffold for their anti-proliferative effect, #40, #41 and their mutants with an altered leucine rich motif to four alanines (shown in figure 8) were synthesized. Since polybasic peptides can be efficiently internalized into cells (24-26) , the peptides were fused with seven Lys (K7; SEQ ID NO:7) via a linker (GGEEAACA; SEQ ID NO:25) at the N-terminus (K7\_#40, K7\_#40M, K7\_#41 and K7\_#41M).--

Please replace the paragraph (Table 3.) beginning at page 64, line 10, with the following:

**--Table 3. SEQUENCE ALIGNMENTS OF THREE ANTIPROLIFERATIVE PEPTIDES WITH NUCLEAR EXCLUSION MOTIFS.**

peptide	sequence ( <u>SEQ ID NO:</u> )*	comment
35	RLRRICSG <u>I</u> LL <u>I</u> RR <u>I</u> LG <u>I</u> IV (1)	
40	RWDPT <u>R</u> LLR <u>F</u> RF <u>L</u> R <u>M</u> LVRRSRPVR (55)	
41	GRGCIFR <u>W</u> RRGLRGM <u>M</u> R <u>L</u> FK (6)	
HIV-1 Rev	<u>L</u> PP <u>L</u> ER <u>L</u> T <u>L</u> D (39)	leu rich motif
HTLV1 Rex	<u>L</u> SAQ <u>L</u> YSS <u>L</u> S <u>L</u> D (41)	leu rich motif
PKI	<u>L</u> ALK <u>L</u> AG <u>L</u> D <u>I</u> N (43)	leu rich but I substutes for L
HDM-2	<u>L</u> SL <u>S</u> <u>F</u> DES <u>L</u> A <u>L</u> C (56)	leu rich but F substitutes for L
general motif	<u>X</u> <u>X</u> <u>X</u> <u>X</u>	X is a hydrophobic residue

\*THE SEQUENCES SHOWN ARE THOSE OF THE RANDOM PEPTIDE LIBRARY MEMBER; ALL WERE FUSED TO THE GFP C-TERMINUS VIA A SPACER SEQUENCE -EEAACA- (SEQ ID NO:13).--

Please replace the paragraph beginning at page 65, line 20, with the following:

--To further examine the action of these peptides in cells, peptides 35, 40 and 41 were synthesized with the N-terminal sequence biotin-GMDELYKEEAAKA- (SEQ ID NO:57). The residues MDELYK (SEQ ID NO:58) were from the C-terminus of GFP; the residues

EEAACA (SEQ ID NO:13) were spacer residues between the GFP beta-can structure and the peptide sequence selected in the functional screen. The GFP beta can was thus replaced with a biotin. Inactive alanine mutant peptides, with all four of the bold residues shown in Table 3 mutated to alanine, were used as controls. A549 cell affinity extracts using the active peptide sequences were compared to control extracts using 1-dimensional silver stained gels. Figure 14 shows the results of this comparison for peptides 41, 40 and 35. Difference bands were identified using MALDI-TOF mass spectrometry and matching the masses of the in-gel digest tryptic peptides to predicted peptide masses for individual proteins using the programs Mascot (Perkins *et al.*, *Electrophoresis* 20:3551-67 (1999)) or Profound (Zhang *et al.*, *Analytical Chemistry* 72:2482-89 (2000)). The resulting identifications, with the number of matching tryptic peptides, are included in the middle columns of Table 4 for peptide 41. Each identified protein had a predicted molecular mass within 10% of the observed mass. Seven interacting proteins, including three subunits of importin-beta, beta-tubulin, BiP, annexin II and calpactin-1/S100, were identified for peptide 41. Each was identified by 10-20 matching tryptic peptides.--

Please cancel the present "SEQUENCE LISTING", pages 1-18, submitted April 15, 2005, and insert therefor the accompanying paper copy of the Substitute Sequence Listing, page numbers 1 to 18, at the end of the application.